STATISTICAL ANALYSIS PLAN

A Phase II Study of the Therapeutic Effects of Epstein-Barr Virus Immune T-Lymphocytes Derived from a Normal HLA-Compatible or Partially-Matched Third-Party Donor in the Treatment of EBV Lymphoproliferative Disorders and EBV-Associated Malignancies

Protocol Number: **11-130**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AID	acquired immunodeficiency
AIDS	acquired immune deficiency syndrome
AE	adverse event
CI	confidence interval
CR	complete response
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
DOR	duration of response
EBV	Epstein-Barr virus
EBV-CTLs	EBV cytotoxic T lymphocytes
EBV-PTLD	EBV post-transplant lymphoproliferative disorder
EBV-LPD	EBV-associated lymphoproliferative disease
LMS	leiomyosarcoma
LPD	lymphoproliferative disease
GvHD	graft-versus-host disease
HLA	human leukocyte antigen
HCT	hematopoietic cell transplant
IPD	important protocol deviation
LLOQ	lower limit of quantification\
NE	not evaluable
NPC	nasopharyngeal carcinoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PID	primary immunodeficiency
PR	partial response
PT	preferred term
PTLD	post-transplant lymphoproliferative disorder
R/R	refractory/relapsed
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SD	stable disease [used in context of response assessment] standard deviation [used in context of analysis methods]
SOC	system organ class
SOT	solid organ transplant
SPR	sustained partial response
tab-cel	tabelecleucel
TESAE	treatment-emergent serious adverse event
TTP	time to progression
TTR	time to response
ULQQ	upper limit of quantification

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses planned for Study 11-130 entitled "A Phase II Study of the Therapeutic Effects of Epstein-Barr Virus Immune T Lymphocytes Derived from a Normal HLA-Compatible or Partially-Matched Third-Party Donor in the Treatment of EBV Lymphoproliferative Disorders and EBV-Associated Malignancies" amended on 15 March 2018 (amendment 23). The investigational product specified in the protocol, ie, Epstein-Barr virus (EBV) immune T-lymphocytes derived from a normal HLA-compatible or partially-matched third-party donor, is referred to as tabelecleucel (tab-cel®, ATA129) throughout this SAP.

The analyses described by this SAP will be performed by the Atara Biostatistics/Programming team unless otherwise specified.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objectives

- To evaluate, in a phase 2 single dose level study, the therapeutic potential of adoptive immunotherapy with tabelecleucel in the treatment of EBV-induced lymphomas and EBV-associated malignancies including EBV^+ Hodgkin's and non-Hodgkin's disease, EBV^+ nasopharyngeal carcinoma (NPC), EBV^+ hemophagocytic lymphohistiocytosis, and EBV^+ leiomyosarcoma (LMS).
- To establish a centralized bank of cryopreserved, Good Manufacturing Practice grade, tabelecleucel which can serve as an immediately accessible source of human leukocyte antigen (HLA) partially matched EBV-specific T cells for adoptive therapy of EBV lymphomas, EBV lymphoproliferative disease (LPD) and other EBV-associated malignancies.
- To estimate the overall survival (OS), disease-free survival, and probability of EBV relapse over time of subjects who receive tabelecleucel.

2.1.2 Secondary Objectives

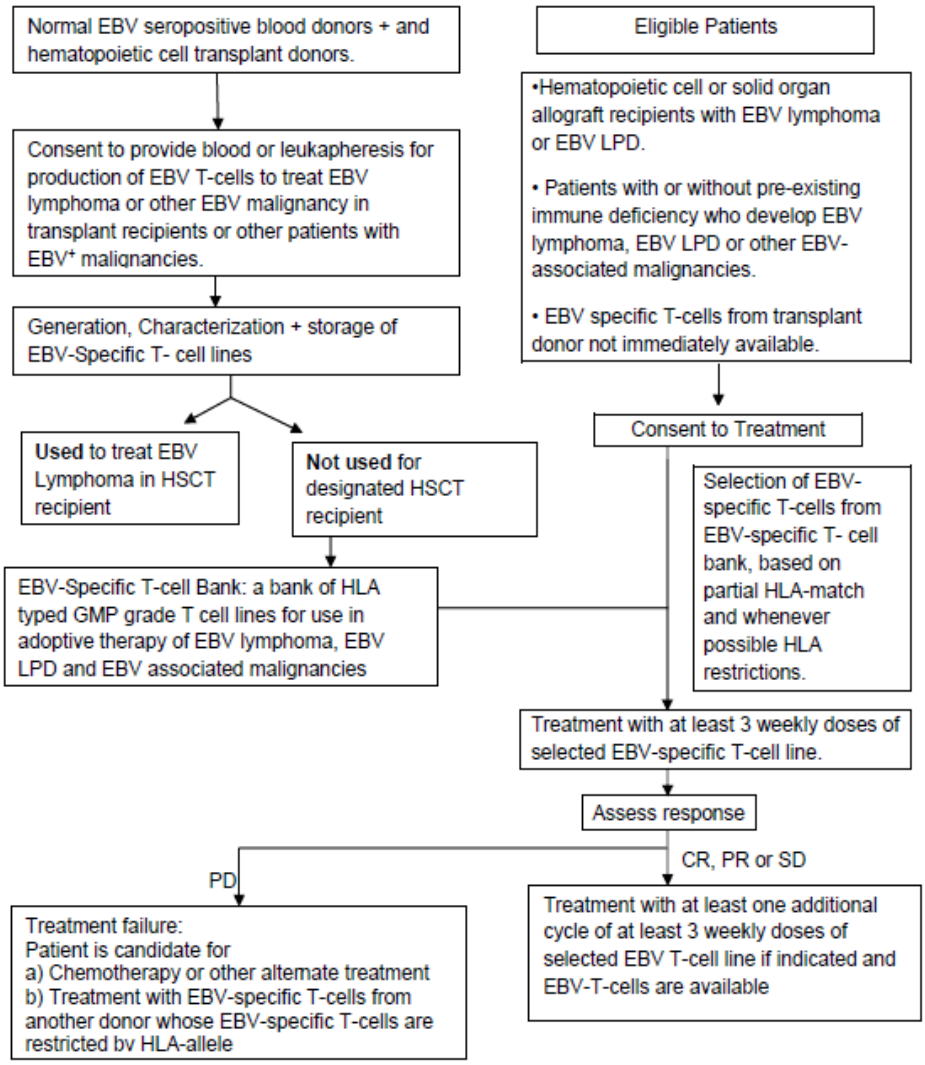
- To evaluate the in vivo expansion and duration of engraftment of successive doses of transferred EBV-reactive lymphocytes within treated subjects and to correlate these findings with the diseased subject's T-cell populations and general immune function.
- To determine the incidence, kinetics and durability of pathological and/or clinical responses of EBV-induced malignancies to treatment with infusions of tabelecleucel.

2.2 Study Design

The study is a non-randomized, single institution phase 2 single dose study, designed to evaluate the therapeutic activity of tabelecleucel when adoptively transferred into subjects with an EBV lymphoma, an EBV$^+$ LPD or another EBV-associated malignancy.

The study schema is presented in Figure 1 below. Please refer to the protocol for details regarding the study design, subject population, treatment and response assessments.

Figure 1 Study Design Chart



Abbreviations: CR, complete response; EBV, Esptein-Barr virus; HLA, human leukocyte antigen; HSCT, hematopoetic stem cell transplant; LPD, lymphoproliferative disease; PD, progressive disease; PR, partial response; SD, stable disease.

The evaluation of treatment will be assessed separately for two groups:

Group 1: Allogeneic marrow graft recipients who are severely immunocompromised and may have more prolonged or sustained T-cell engraftment or subjects with severe congenital or antineoplastic drug induced immunodeficiency who could be durably engrafted. Subjects in this cohort are at risk for graft-verus-host disease (GvHD).

Group 2: Organ allograft recipients who can reject third party blood cells although immunocompromised, subjects with acquired immune deficiency syndrome (AIDS) who will almost invariably reject the infused T cells, or subjects who developed other EBV-associated malignancies without pre-existing immune deficiency who are also expected to reject the infused T cells. The subjects in this cohort are at low or no risk of GvHD.

In this study, subjects could change to tabelecleucel with a different HLA restriction from a different donor either due to a lack of efficacy from the current cell-line or insufficient supply. Only the change to tabelecleucel with a different HLA restriction due to lack of efficacy is considered as treatment switch ("Restriction Switch").

2.3 Sample Size

2.3.1 Planned Rationale for Sample Size

For subjects in group 1 who have an EBV-LPD, a maximum of 28 subjects will be accrued in study, in a 2-stage design. The therapy is considered active if the probability of a complete response (CR) or sustained partial response (SPR) for 6 months in the population exceeds 0.40. In the first stage, 16 subjects will be enrolled in the study. If 6 or fewer CR/SPRs are observed, then the study will be stopped. If at least 7 CR/SPRs are observed, then 12 additional subjects will be accrued for a total of 28 subjects. At the conclusion of the study, if 14 or fewer CR/SPRs are observed, the treatment will be considered not sufficiently active. This design has 90% power for a population with CR/SPR proportion of 0.64 using a one-sided test with type I error rate of $\alpha = 0.10$.

Subjects in group 2 who develop an EBV-LPD as a complication of an organ allograft or AIDS and subjects with EBV-associated malignancies without pre-existing immune deficiency are expected to consistently reject the third party cells. As a result, the survival of cells after each infusion is expected to be shorter. Nevertheless, an initial expansion suggests that 50-70% of these subjects may achieve a durable CR or partial response (PR). Therefore, for this group, a two-stage design will also be adopted, with a maximum of 28 subjects accrued onto this study. The therapy is considered active if the probability of a CR/SPR for 6 months in the population exceeds 0.20. If at the conclusion of the study 9 or more of the 28 subjects remain disease free for 6 months from the start of treatment, then the treatment will be considered active. These circumstances under which the treatment will be considered active are based on a one-sided test with type I error rate of $\alpha = 0.10$. The study design has 90% power for a population with CR/SPR proportion of 0.40.

Based on responses observed following enrollment of 43 subjects across the 2 groups, the protocol was amended to allow enrollment of an additional 28 subjects in each group after the initial planned subject accrual is complete and the stopping boundaries have not been met. These additional subjects will provide a more precise estimate of the CR/SPR rate in the two subject populations. With 56 subjects in each group, the probability of a CR/SPR can be estimated to within ± 0.13 with 95% confidence.

2.3.2 Actual Sample Size

A total of 87 subjects with EBV^+ disease were enrolled in the study.

3 STUDY ENDPOINTS

Response-related efficacy endpoints were not specified in the protocol and are, therefore, defined in this SAP. All of the efficacy analyses of response-related endpoints will be based on the disease assessments performed by the investigator.

3.1 Primary Endpoint

The primary endpoint is objective response rate (**ORR**), which is defined as the proportion of subjects who have achieved a CR or PR during the study.

3.2 Secondary Endpoints

- Overall survival (OS)
- Duration of response (DOR)
- Progression-free survival (PFS)
- Durable response rate (DRR)
- Time to progression (TTP)
- Time to response (TTR)

The definition of these secondary endpoints will be provided in Section 8.2.

4 ANALYSIS SETS AND SUBGROUPS

In general, summary tables will include only the subjects in the Full Analysis Set defined in Section 4.1 or subgroups defined in Section 4.3. Cohorts and combined cohorts will be presented as columns in the summary tables .

4.1 Full Analysis Set

The Full Analysis Set is defined as all subjects who received at least one dose of tabelecleucel. All efficacy and safety analyses will use the Full Analysis Set except for the endpoints of DOR and TTR, which will be conducted on the subjects in the Full Analysis Set who achieved an objective response (CR or PR).

4.2 Subject Cohorts

Analysis cohorts are defined based on subjects' disease histology, prior EBV related disease therapy and source of donors of study treatment received. The cohort definition is specified in the following table. Final cohorts to be used in the analysis will depend on the availability of the data.

All the analyses will be presented by cohorts or combined cohorts defined in this SAP, not by the groups defined in the protocol.

Table 1: Cohorts

Cohort Number	Cohort Name	Subjects enrolled in The Study
1	Tab-cel HCT EBV$^+$ PTLD R/R Rituximab	Y
2	Tab-cel HCT EBV$^+$ PTLD Rituximab Naïve	N
3	Tab-cel SOT EBV$^+$ PTLD R/R Rituximab	Y
4	Tab-cel SOT EBV$^+$ PTLD R/R Rituximab + Chemo	Y
5	Tab-cel AID LPD	Y
6	Tab-cel PID LPD	Y
7	Tab-cel Lymphoma	Y
31	Tab-cel LMS	Y
32	Tab-cel NPC	Y
61	Tab-cel Other Solid Tumor	Y
71	Tab-cel Viremia	Y
101	EBV-CTL (Transplant donor derived) HCT EBV$^+$ PTLD R/R Rituximab	N
102	EBV-CTL (Transplant donor derived) HCT EBV$^+$ PTLD Rituximab Naïve	N
103	EBV-CTL (Transplant donor derived) SOT EBV$^+$ PTLD	N
106	EBV-CTL (Transplant donor derived) PID LPD	N

Table 1: Cohorts

Cohort Number	Cohort Name	Subjects enrolled in The Study
107	EBV-CTL (Transplant donor derived) Lymphoma	N
171	EBV-CTL (Transplant donor derived) Viremia	N
201	Autologous	N

Abbreviations: AID, acquired immunodeficiency; chemo, chemotherapy; CTL, cytotoxic T lymphocyte; EBV, Epstein-Barr virus; HCT, hematopoietic cell transplant; LMS, leiomyosarcoma; LPD, lymphoproliferative disorder; N, no; NPC, nasopharyngeal carcinoma; PID, primary immunodeficiency; PTLD, post-transplant lymphoproliferative disorder; R/R, refractory/relapsed; SOT, solid organ transplant; Tab-cel, tabelecleucel; Y, yes

Disposition, demographics, baseline characteristics, exposure and safety will be summarized as in the following headers:

HCT/SOT EBV$^+$ PTLD

Tab-cel HCT EBV$^+$ PTLD	Tab-cel SOT EBV$^+$ PTLD			Total
R/R Rituximab (Cohort 1)	R/R Rituximab (Cohort 3)	R/R Rituximab+Chemo (Cohort 4)	Total	

Other EBV$^+$ Disorders with Immunodeficiency (ID)

Tab-cel AID LPD (Cohort 5)	Tab-cel PID LPD (Cohort 6)	Tab-cel Viremia (Cohort 71)	Tab-cel LMS (Cohort 31)	Total

EBV$^+$ Malignancy without Immunodeficiency (ID) and Overall

Tab-cel EBV$^+$ Malignancy without ID				Tab-cel HCT/SOT EBV$^+$ PTLD	Tab-cel Other EBV$^+$ Disorders with ID	Overall Total
Lymphoma (Cohort 7)	NPC (Cohort 32)	Other solid tumor (Cohort 61)	Total			

Efficacy will be summarized as in the following headers:

HCT/SOT EBV+ PTLD

Tab-cel HCT EBV+ PTLD	Tab-cel SOT EBV+ PTLD		
R/R Rituximab (Cohort 1)	R/R Rituximab (Cohort 3)	R/R Rituximab+Chemo (Cohort 4)	Total

Other EBV+ Disorders with Immunodeficiency (ID)

Tab-cel AID LPD (Cohort 5)	Tab-cel PID LPD (Cohort 6)	Tab-cel Viremia (Cohort 71)	Tab-cel LMS (Cohort 31)

EBV+ Malignancy without Immunodeficiency (ID)

Tab-cel Lymphoma (Cohort 7)	Tab-cel NPC (Cohort 32)	Tab-cel Other Solid Tumor (Cohort 61)

4.3 Subgroups

Some of the safety and efficacy analyses will be repeated for the following subgroups within the Full Analysis Set.

- Age (< 16 vs. ≥ 16; 18 vs. ≥ 18)
- Gender (male vs. female)
- Race (White, other races, unknown or missing)

5 INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

No formal interim analysis is planned.

6 GENERAL PRINCIPLES

6.1 General

Unless otherwise specified, all continuous variables will be summarized using descriptive statistics, which will include the number of subjects with a valid measurement (n), mean, standard deviation (SD), median, 25% quantile, 75% quantile, minimum and maximum. All categorical variables will be summarized using frequencies and percentages. The exact binomial 2-sided 95% confidence interval (CI) will be provided for all binary efficacy endpoints,

including ORR and DRR. Kaplan-Meier (K-M) estimates along with their corresponding 95% CI will be calculated for time-to-event endpoints including OS, PFS, DOR and TTP.

The following terms may be used for this SAP and tables, figures and listings (TFLs):

- **Study treatment:** In this monotherapy study, study treatment refers to tabelecleucel.
- **Enrolled subjects:** Enrolled subjects refers to the subjects who receive study treatment.
- **Enrollment date:** Enrollment date is the date the inform consent form was signed.
- **Study day:** The subject's time on study will be determined in study days. Study day 1 is defined as the day of the first tabelecleucel administration. Study day is defined as the date of interest minus study day 1 plus 1 if the date is on or after the study day 1. If the date is before study day 1, the study day is defined as the date of interest minus study day 1.
- **Baseline:** Baseline in general refers to study day 1 prior to the first administration of tabelecleucel. The baseline value of a parameter (e.g., laboratory tests and efficacy endpoints) is defined as the value immediately prior to receiving the first tabelecleucel administration.
- **Duration of treatment:** The duration of treatment is defined as the date of the last dose of tabelecleucel minus the date of the first dose of tabelecleucel plus 1
- **Treatment exposure period:** from study day 1 through 30 days after the last administration of tabelecleucel.
- **Restriction Switch:** Subjects could change to tabelecleucel with a different HLA restriction from a different donor either due to a lack of efficacy from the current cell line or insufficient supply. "Restriction switch" refers to only the change to tabelecleucel with a different HLA restriction due to lack of efficacy.
- **Year:** A year consists of 365.25 days
- **Month:** A month consists of 365.25/12 days

6.2 Missing Data Handling

In general, missing data will not be imputed. Only year of birth was collected during the study. To calculate age, 01 July was used to impute the birth day and month.

6.3 Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit. When a single value is needed, the following rule(s) will be used:

- In general, the baseline value will be the last non-missing value on or prior to the first dose date of study treatment, unless specified differently.

- For post-baseline visits, if there are multiple assessments in a same visit window, the assessment closest to the corresponding dose date will be used in the analysis. For example, if after cycle 1 Infusion 1 (day 1) laboratory samples are collected on day 3 and day 5 before cycle 1 Infusion 2 which is on day 8, the laboratory assessment collected on day 3 will be used for cycle 1 Infusion 1.

For summary of laboratory data by visit window, it is possible that large time gaps exist between dosing cycles. To acount for this, a cycle starts at the first dose of the cycle and ends at the day before the first dose of the next cycle or first dose of the cycle + 50 days, whichever is earlier. For the last cycle for a subject, the cycle ends at first dose of the cycle + 50 days or last dose of the cycle + 30 days, whichever is earlier. Within a cycle, additional visits may be defined based on the actual infusion date of each dose. The window of an infusion visit starts at the infusion date and ends at the day before the next infusion date. If an infusion is the last infusion for a cycle, the infusion visit window ends at the day before the start of next cycle or the infusion date + 27 days, whichever is earlier.

Disease assessments performed by investigator will be grouped into one visit if the gap between two consecutive assessments is less than or equal to 14 days.

6.4 Data Handling and Electronic Transfer of Data

Data files will be provided from the site via secured transfer. The data will be mapped from the raw files to the fields available in the clinical study database. The formatting of the data into data entry packets will be done in accordance with Atara Work Instruction. The data will then be transferred via secured server to the vendor for entry into the study database using the vendor's standard operating procedures (SOP) and data entry conventions.

Study Data Tabulation Model (SDTM) data will be derived from raw data entered into the clinical study database. Analysis Data Model (ADaM) data will be derived from the SDTM data for statistical analyses.

6.5 Validation of Statistical Analysis

The statistical analysis validation will be conducted in accordance with Atara's SOP.

7 STUDY SUBJECTS

7.1 Study Disposition

Subject disposition, including the number of subjects screened, the number of subjects deemed eligible and the number of subjects enrolled/treated, will be summarized. Treatment status (completed or discontinued) with reasons for treatment discontinuation and end of study status (completed or discontinued) with reasons for study discontinuation will also be summarized. The analysis will be repeated for the subgroups defined in Section 4.3.

7.2 Important Protocol Deviations

Important protocol deviations (IPDs) will be reviewed prior to the final database lock. A by-subject listing of IPDs will be provided, which will include IPD category and description.

7.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics for the Full Analysis Set will be summarized. Similar summary will be conducted by subgroups defined in Section 4.3.

- Age at baseline: descriptive statistics and n (%) for the following:
    - < 2, 2 to < 12, 12 to < 16, 16 to < 65, and ≥ 65 years
    - < 16 and ≥ 16 years
    - < 2, 2 to < 12, 12 to < 18, 18 to < 65, and ≥ 65 years
    - < 18 and ≥ 18 years
- Sex (male vs. female)
- Ethnicity (Hispanic vs. non-Hispanic)
- Race (Asian, Black or African American, White, other, or unknown)
- Karnofsky (age ≥ 16 only): descriptive statistics and n (%)
- Lansky score (age < 16 only): descriptive statistics and n (%)
- Time from initial EBV related disease diagnosis to first dose of tabelecleucel (months)

The following disease characteristics at baseline will be summarized for subjects with hematopoetic cell transplant (HCT) or solid organ transplant (SOT) EBV^+ post-transplant post-transplant lymphoproliferative disorder (PTLD).

- Disease risk subgroups (for subjects ≥ 16 years and ≥ 18 years)
    a) Age < 60 years (low risk); ≥ 60 years (high risk)
    b) Karnofsky score ≥ 80 (low risk); Karnofsky score ≤ 70 (high risk)
    c) Serum LDH concentration: normal (low risk); elevated (>upper limit of normal, high risk)
    d) PTLD-adapted prognostic index (Choquet 2007): Low risk (no high risk factor among items a to c); low-intermediate risk (1 high risk factor among items a to c); high risk (2 or 3 high risk factors)
- EBV^+ PTLD disease confirmed by pathology
- Time from transplant to diagnosis of EBV^+ PTLD
- Central nervous system (CNS) disease
- Extranodal disease (including bone marrow)

- Lymph node disease
- ≥ 3 sites of disease

7.4 Extent of Exposure

Descriptive statistics will be provided for average number of weight-adjusted cells per dose (10^6 cells/kg), number of lots subjects received, number of treatment cycles, number of doses, and duration of treatment (date of last dose of tabelecleucel – date of first dose of tabelecleucel + 1). Summary and listing of the subjects who undergo Restriction Switch will also be provided.

The analysis will be repeated for the subgroups defined in Section 4.3

8 EFFICACY ANALYSES

For the primary efficacy analysis, all response assessment data will be included regardless of how many Restriction Switches the subject had.

Efficacy analyses will be conducted by cohorts and combined cohorts specified in Section 4.2.

Disease assesments performed by investigators regardless of modalities will be grouped into one timepoint assessment if the gap between two consecutive disease assessments is less than or equal to 14 days. This grouping will continue for the same timepoint assessment until the gap between two consecutive disease assessments exceeds 14 days.

The ranking for assessment modalities is specified in Table 2. If there are multiple assessments with the same modality in the same timepoint assessment, the worst/worse assessment (from the best to the worst in the order of not evaluable [NE], CR, PR, stable disease [SD] and progressive disease [PD]) will be selected for that modality. If there are assessments based on multiple modalities for a timepoint assessment, then the overall response for the timepoint assessment will be decided by the rank of the modalities specified in Table 2. For example, for a timepoint assessment, a PR was assessed per biopsy and a CR was assessed per physical examination. The assessement per biopsy will override that of physical examination for this timepoint assessment. If PD is determined as the response for a timepoint assessment, the earliest assessment date among all the disease assessments for this timepoint assessment will be considered as the PD date. If SD, PR or CR is determined as the response for a time assessment, the latest assessment date among all the disease assessments for this timepoint assessment will be considered as the response date.

While in general if any therapy directed towards the disease being treated, other than protocol-specified treatment, is initiated, response data after the initiation date of such therapy may be censored. However, given the fact that some anti-underlying disease therapies were actually allowed per the protocol, in the primary analysis of disease assessment related endpoints, none of such therapies were considered for censoring rule. As a sensitivity analysis,

response data after the initiation of such therapies are censored, and such analysis is conducted for the endpoints including ORR, DOR, and PFS based on the Full Analysis Set.

Table 2: Rank of the Modalities (1 indicates highest rank)

Modality	Priority for Non-Viremia	Priority for Viremia
BIOPSY	1	1
PATHOLOGY	1	1
BONE MARROW	1	1
PET	2	2
PET SCAN	2	2
PET/CT SCAN	2	2
CT SCAN	2	2
MRI	2	2
ULTRASOUND	3	3
THALLIUM SCAN	4	4
PHYSICAL EXAM	4	4
BLOOD	4	1
CLINICAL LABORATORY TESTS	4	4

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

8.1 Analysis of Primary Endpoints

The primary endpoint ORR and its corresponding 95% CI will be reported by cohorts and combined cohorts specified in Section 4.3. The primary endpoint ORR is the proportion of subjects who have achieved a CR or PR during the study.

Sensitivity analysis will be conducted for ORR excluding response data after the initiation of any non-protocol anti-underlying disease therapies.

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8.2 Analysis of Secondary Endpoints

8.2.1 Overall Survival

Overall survival is defined as the time from the first dose of tabelecleucel to the date of death for any cause. Subjects who are lost to follow-up or still alive will be censored on the last known-to-be-alive date. All data including those collected during the follow-up period, if any, will be summarized.

8.2.2 Duration of Response

Duration of response is calculated based on subjects who achieve CR or PR. DOR is defined as the time from the date of initial response until (1) progression after the last response or (2) death due to any cause.

Only deaths within 90 days after the last valid disease evaluation (ie, not NE) will be counted as events in the DOR definition above.

For subjects without an event of death or disease progression, DOR is censored at the last valid (not NE) disease evaluation date.

In a sensitivity analysis, if any anti-underlying disease therapy is initialized before the event date/censoring date, DOR is censored at the last assessment date prior to the therapy initialization.

8.2.3 Progression-free Survival

Progression-free survival is defined as the time from the first dose of tabelecleucel to either of following events, whichever occurs first: (1) progression after the last response or (2) death due to any cause.

Death within 90 days after last valid disease evaluation (ie, not NE), or first dose date of tabelecleucel if there is no valid post-baseline disease evaluation, will be counted as events in the PFS definition above.

For subjects without event per the definition above, PFS will be censored at

- Last valid (not NE) post-baseline disease evaluation date, or
- First dose date if there is no valid post-baseline disease evaluation

As a sensitivity analysis, PFS will be defined as the time from the first dose of tabelecleucel to either of following events, whichever occurs first, (1) the first progression or (2) death due to any cause. All other details and censoring rules are the same as above for the primary PFS analysis.

In another sensitivity analysis, if any anti-underlying disease therapy is initialized before the event date/censoring date, PFS is censored at the last assessment date prior to the therapy initialization.

8.2.4 Durable response rate

A response with a duration > 6 months is considered a durable response, and the durable response rate (DRR) is defined as the proportion of subjects in the Full Analysis Set with a durable response.

Summary will also be provided for clinical benefit rate which is defined as the proportion of subjects who have achieved a CR, PR or SD assessed at least 28 days after the first dose date of tabelecleucel.

8.2.5 Time to Progression

Time to progression (TTP) is defined as the time from the date of the first dose of tabelecleucel to progression after the last response. Death within 90 days after the last valid post-baseline disease evaluation, or after first dose date if there is no valid post-baseline disease evaluation, will be counted as an event only if the death reason is due to disease progression. Data will be censored on the death date if such deaths are not due to disease progression. The other censoring rules are the same as the ones used for the primary analysis of PFS in Section 8.2.3.

8.2.6 Time to Response

Time to response (TTR) is calculated only for subjects who achieve CR or PR on study. TTR is defined as the time from the date of the first dose of tabelecleucel to the date of the response (PR or CR whichever occurs first). Descriptive statistics will be provided. Similarly, time to best response will also be summarized for subjects who achieve CR or PR.

8.3 Subgroup Analysis

The analysis of ORR and OS will be repeated for the subgroups defined in section 4.3.

9 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

No pharmacokinetic/pharmacodynamic analysis is planned.

10 SAFETY ANALYSIS

10.1 Summary of Adverse Events

Only serious adverse events (SAEs) were systematically collected in this study, hence all adverse event (AE) summaries will be based on SAEs only. Non-serious AEs will be listed if any.

The Medical Dictionary for Regulatory Activities version 22.0 will be used to code the SAEs to a system organ class (SOC) and a preferred term (PT) within the SOC. The Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 was used to grade the severity of SAEs.

Treatment-emergent serious adverse events (TESAEs) are defined as follows:

- Any SAE occurring after initiation of the first dose of tabelecleucel through 30 days after the last administration of tabelecleucel, or
- Any SAE occurred prior to the first dose but worsened after the first dose of tabelecleucel or
- Any related SAE with date of onset on or after first dose of tabelecleucel

SAEs occurring on the same day as the first dose of tabelecleucel will be counted as treatment-emergent.

All SAEs collected in this study will be listed. But only TESAEs will be summarized as follows:

- Overall summary of subject incidence for the following TESAE categories (repeated for the subgroups listed in Section 4.3)
    - Any TESAEs
    - TESAEs with worst grade ≥ 3
    - Fatal TESAEs
    - Any Treatment related TESAEs
    - Treatment related TESAEs with worst grade ≥ 3
    - Treatment related Fatal TESAEs
- Subject incidence of the following categories of TESAEs will be summarized by PT in descending order of frequency
    - TESAEs (repeated for the subgroups listed in Section 4.3)
    - Treatment-related TESAEs (repeated for < 16 vs. ≥ 16 and < 18 vs. ≥ 18 years age subgroups)
    - Fatal TESAES (repeated for < 16 vs. ≥ 16 and < 18 vs. ≥ 18 years age subgroups)
    - Treatment-related fatal TESAE
- Subject incidence rates of the following categories of TESAEs will be summarized by PT and worst grade
    - TESAEs
    - TESAEs with worst grade ≥ 3
    - Treatment-related TESAEs
- Subject incidence of the following categories of TESAEs will be summarized separately in descending order of frequency by SOC and then PT within an SOC:
    - TESAEs
    - Treatment-related TESAEs

Primary cause of all deaths will be summarized.

10.2 Summary of Laboratory Results

Routine clinical laboratory data (ie, hematology and serum chemistry) will be processed by local laboratories. Atara Biotherapeutics will convert the original test results/units to standard and conventional results/units and grade laboratory test results based on the CTCAE version 4.03 grading and corresponding reference ranges from University of California San Francisco[1] for the laboratory parameters.

In case the laboratory test result is less than the lower limit of quantification (LLOQ), a value of half the LLOQ will be used as the numerical test result. If the laboratory test result is greater than the upper limit of quantification (ULOQ), the ULOQ will be used as the numerical test result.

10.2.1 General Presentation of Laboratory Data

Summary of selected laboratory tests (Appendix 13.1 Selected Laboratory Tests) will include only data collected up to the last dose of study treatment plus 30 days.

For selected laboratory parameters, descriptive statistics of actual values and changes from baseline for the post-baseline laboratory data will be summarized for each visit window. Descriptive statistics of the minimum and maximum post baseline values for each subject will also be summarized. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 6.3. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

The percentage of change from baseline (mean ± SD) for selected lab parameters vs. visit window, will be plotted.

In addition, grade shift tables from baseline to worst on-treatment value will be provided for selected laboratory parameters.

For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

In addition, data for sirolimus, tacrolimus and interleukin 6, highly sensitive will be provided in listings.

10.2.2 Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase by at least 1 toxicity grade from baseline at any post baseline time point, up to and including the date of last dose of tabelecleucel plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least grade 1 observed at any post baseline time point up to and including the date of last dose of tabelecleucel plus 30 days will be considered treatment emergent.

[1] Available at: http://labmed.ucsf.edu/sfghlab/test/ReferenceRanges.html

Number of subjects (%) with treatment emergent laboratory abnormalities will be summarized for selected laboratory parameters (Appendix 13.1 Summery of Selected Laboratory Tests). The number of subjects with any post baseline value for each laboratory test will be the denominator for the percentage of subjects with the corresponding treatment-emergent laboratory abnormality.

10.3 Exposure to Prior/Concomitant/Subsequent Therapies

Number of lines of prior systemic EBV related disease therapies and numbers of subjects who received different prior therapies as below will be summarized:

- Rituximab monotherapy
- Chemotherapy
    - Anthracycline-based therapy (CHOP/R-CHOP)
    - Brentuximab vedotin
    - Plantinum-based therapy
    - Gemicitabine-based therapy
    - Other
- Radiotherapy
- Other therapy
    - Surgery/procedure
    - T-cell therapy
    - Stem cell transplant
    - Checkpoint inhibitor
    - Other

The concomitant and post treatment therapies will be provided in a listing. Therapies which overlapped with the study treatment duration will be considered as concomitant therapies. Therapies which started after last dose of study treatment or started during study treatment and continued after last dose will be considered as post treatment therapies. If a therapy can not be categorized due to missing dates, the during or post study treatment flags provided in the study database will be used to identify concomitant and post-treatment therapies, respectively.

Number (%) of subjects with concomitant immunosuppressive medications will be provided for subjects with HCT or SOT EBV^+ PTLD and LMS.

10.4 Pregnancies

No data for pregnancies are available in this study.

11 CHANGES FROM PROTOCOL SPECIFIED ANALYSES

This study was designed and performed at a single academic center. Atara adjusted the endpoints and analysis approaches as follows:

- No formal hypothesis test will be conducted on CR/SPR although the sample size calculation is a two-stage design based on CR/SPR. Point estimates and CIs will be provided for ORR for the cohorts and combined cohorts defined in Section 4.3 whenever feasible. In addition, statistics for DOR, PFS, DRR, TTP and TTR are also provided.
- In the protocol, the primary endpoint is CR or a SPR for 6 months. To be consistent with Atara's other tabelecleucel studies, ORR is considered as the primary endpoint.
- All the analyses will be presented by the cohorts and cohorts combined defined in this SAP (Section 4.2), not by the groups defined in the protocol Section 9.0.

12 REFERENCES

Choquet S, Oertel S, LeBlond V, et al. Rituximab in the management of post-transplantation lymphoproliferative disorder after solid organ transplantation: Proceed with caution. Ann Hematol 2007; 86: 599–607

13 APPENDIX

13.1 Summary of Selected Laboratory Tests

Laboratory Test	Direction of Abnormality	Summary ofTreatment-emergent Abnormality and Grade Shift Table	Summary of Laboratory Test Value by Visit window
WBC COUNT	decreased	Y	Y
PLATELETS	decreased	Y	Y
ABSOLUTE NEUTROPHIL	decreased	Y	Y
ABSOLUTE LYMPHOCYTE	increased and decreased	Y	Y
LACTATE DEHYDROGENASE (LDH)	Not applicable	Not applicable	Y
HEMOGLOBIN	increased and decreased	Y	Y
CREATININE	increased	Y	Y
TOTAL BILIRUBIN	increased	Y	Y
ALBUMIN	decreased	Y	Y
ASPARTATE AMINOTRANSFERASE (AST)	increased	Y	Y
ALANINE AMINOTRANSFERASE (ALT)	increased	Y	Y
ALKALINE PHOSPHATASE (ALK)	increased	Y	Y
SIROLIMUS	Not applicable	Not applicable	Y
TACROLIMUS	Not applicable	Not applicable	Y